SUPPORTING INFORMATION

for
the
communication
entitled

A Highly Stereoselective Synthesis of Chiral α-Amino-β-Lactams via the Kinugasa Reaction Employing Ynamides.

authored by

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GENERAL EXPERIMENTAL INFORMATION

All reactions were performed in flame-dried glassware under nitrogen atmosphere. Solvents were distilled prior to use. Reagents were used as purchased from Aldrich, Acros, Alfa Aesar, or TCI) unless otherwise noted. Chromatographic separations were performed using Silicycle 43-60 Å SiO_2. ^{1}H and ^{13}C NMR spectra were obtained on Varian VI-400 and VI-500 spectrometers using $CDCl_3$ with TMS or residual solvent as standard unless otherwise noted. Melting points were determined using a Laboratory Devices MEL-TEMP and are uncorrected/calibrated. Infrared spectra were obtained on Bruker EQUINOX 55 FTIR. TLC analysis was performed using Aldrich 254 nm polyester-backed plates (60 Å, 250 μm) and visualized using UV and $KMnO_4$ stains. Low-resolution mass spectra were obtained using an Agilent 1100 series LS/MSD and are APCI. High-resolution mass spectral analysis performed at University of Wisconsin School of Pharmacy and Department of Chemistry Mass Spectrometry Laboratories. X-Ray analysis performed at University of Minnesota Department of Chemistry X-Ray facility. All spectral data obtained for new compounds are reported here.

General Procedure for Preparations of Ynamides 8, 9, and 11.[1,2]

Copper catalyzed coupling of amides and 1-bromo-2-triisopropylsilylacetylene: To a mixture of amide (1.0 equiv), K_2CO_3 (2.5 equiv), $CuSO_4 \bullet 5H_2O$ (0.15 equiv), and 1,10-phenanthroline (0.3 equiv) in a reaction vial were added 1-bromo-2-triisopropylsilylacetylene (1.0-1.5 equiv) and toluene (5 mL for every 2.0 mmol of the amide). The reaction mixture was placed under a blanket of nitrogen and heated in an oil bath at 65-85 °C for 48 h while being monitored with TLC analysis. Upon completion, the reaction mixture was cooled to rt, diluted with EtOAc, and filtered through Celite™. The filtrate was concentrated *in vacuo*. The crude products were purified by silica gel flash column chromatography [gradient eluent: EtOAc in hexane] to afford the respective TIPS protected ynamides.

Deprotection of TIPS-acetylene: To a solution of TIPS protected ynamide (1.0 equiv.) in anhydrous THF (5 mL for every 1 mmol of ynamide) stirring at 0 ^oC was added 1.5 equiv. of TBAF (1M solution in THF) via syringe over a period of 5 minutes. The resulting solution was stirred at 0 ^oC. After TLC indicated that the starting material was completely consumed, the solution was concentrated *in vacuo*, silica gel chromatography with EtOAc/hexane gave the respective terminally unsubstituted ynamides.

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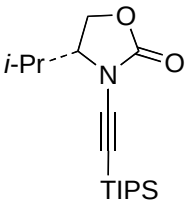
1. Zhang. X.; Zhang, Y.; Huang, J.; Hsung, R. P.; Kurtz, K. C. M.; Oppenheimer, J.; Petersen, M. E.; Sagamanova, I. K.; Shen, L.; Tracey, M. R. *J. Org. Chem.* **2006**, *71*, 4170.
2. Zhang, Y.; Hsung, R. P.; Tracey, M. R.; Kurtz, K. C. M.; Vera, E. L. *Org. Lett.* **2004**, *6*, 1151.

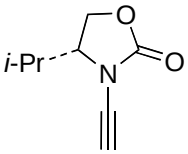
CHARACTERIZATIONS



S1

Ynamide **S1** was prepared from corresponding oxazolidone (1 g, 7.7 mmol) and 1-bromo-2-triisopropylsilylacetylene (2.01 g, 7.7 mmol) following general coupling procedure. Reaction gave **S1** (226 mg, 0.73 mmol) in 10% unoptimized yield.

R_f = 0.85 [25% EtOAc in hexanes]; brown oil; $[\alpha]_D^{20}$ = - 30.0 (*c* 13.4, CH_2Cl_2); IR (film) cm^{-1} 2944(m), 2886(m), 2361(w), 2183(m), 1775(s), 1464(m), 1402(s), 1183(m); ^1H NMR (400 MHz, $CDCl_3$) δ 0.09-1.00 (m, 6 H), 1.05-1.08 (m, 21 H), 2.22 (dsept, 1 H, *J* = 4.0, 14.0 Hz), 3.97 (ddd, 1 H, *J* = 4.0, 6.0, 10.0 Hz), 4.13 (dd, 1 H, *J* = 6.0, 8.8 Hz), 4.36 (t, 1 H, *J* = 9.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.4, 15.4, 17.3, 18.8, 29.4, 62.0, 65.0, 71.2, 92.9, 156.2; mass spectrum (ESI): m/e (% relative intensity) 310.2 (100) $(M + H)^+$; m/e calcd for $C_{17}H_{32}NO_2Si^+$ 310.2197, found 310.2203.

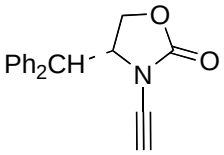


8

Ynamide **8** was prepared from **S1** (1.5 g, 4.85 mmol) following general deprotection procedure. Deprotection gave **8** (476 mg, 3.1 mmol) in 64% unoptimized yield.

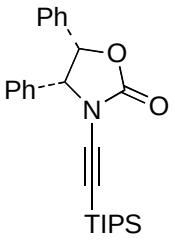
R_f = 0.34 [25% EtOAc in hexanes]; yellow oil; $[\alpha]_D^{20}$ = - 47.7 (*c* 8.63, CH_2Cl_2); IR (film) cm^{-1} 3308(w), 2972(w), 2880(w), 2153(m), 1772(s), 1484(m), 1403(m), 1095(m); ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (dd, 6 H, *J* = 3.2, 6.8 Hz), 2.14 (dsept, 1 H, *J* = 4.0, 7.2

Hz), 2.82 (s, 1 H), 3.93 (ddd, 1 H, *J* = 4.0, 5.2, 9.6 Hz), 4.08 (dd, 1 H, *J* = 5.6, 9.2 Hz), 4.33 (t, 1 H, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.3, 17.3, 29.2, 61.1, 61.6, 65.2, 72.4, 156.6; mass spectrum (ESI): m/e (% relative intensity) 153.1 (83) M^+, 66.1 (100); m/e calcd for $C_8H_{11}NO_2^+$ 153.0785, found 153.0785.



9

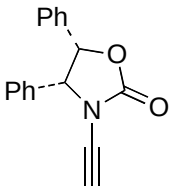
Ynamide **9** was prepared from TIPS-substituted ynamide (730 mg, 1.69 mmol) following general deprotection procedure. Deprotection gave **9** (440 mg, 1.6 mmol) in 95% yield. R_f = 0.25 [25% EtOAc in hexanes]; mp 109-110 °C; $[\alpha]_D^{20}$ = -203.6 (*c* 0.5, CH_2Cl_2); IR (film) cm^{-1} 3265(w), 2152(w), 1752(s), 1493(w), 1472(w), 1453(w), 1407(m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.75 (s, 1 H), 4.25 (dd, 1 H, *J* = 5.2, 9.0 Hz), 4.49-4.55 (m, 2 H), 4.84 (ddd, 1 H, *J* = 5.2, 6.4, 8.4 Hz), 7.20-7.36 (m, 10 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.8, 59.7, 62.0, 66.4, 71.8, 127.5, 127.7, 128.4, 128.6, 128.8, 129.0, 138.2, 139.3, 155.8; mass spectrum (APCI): m/e (% relative intensity) 278.1 (100) $(M + H)^+$.



S2

Ynamide **S2** was prepared from the corresponding oxazolidone (1.48 g, 6.23 mmol) and 1-bromo-2-triisopropylsilylacetylene (2.44 g, 9.35 mmol) following general coupling procedure. The coupling reaction gave **S2** (2.44g, 5.8 mmol) in 93% yield.

R_f = 0.68 [33% EtOAc in hexanes]; mp 128-129 °C; $[\alpha]_D^{20}$ = - 139.6 (*c* 1.24, CH_2Cl_2); IR (film) cm^{-1} 3035(w), 2864(w), 2183(m), 1750(s), 1455(m), 1385(m), 1192(m), 1124(m), 1078(w), 1021(m), 998(w), 921 (w), 882(m), 850(m); ^1H NMR (400 MHz, $CDCl_3$) δ 0.89-0.92 (m, 21 H), 5.37 (d, 1 H, *J* = 8.2 Hz), 5.93 (d, 1 H, *J* = 8.2 Hz), 6.89-6.92 (m, 2 H), 6.94-6.96 (m, 2 H), 7.11-7.13 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.3, 18.6, 67.6, 71.8, 80.8, 92.8, 126.3, 127.9, 128.3, 128.4, 128.6, 128.8, 132.7, 133.8, 155.9; mass spectrum (ESI): m/e (% relative intensity) 442.2 (100) $(M + Na)^+$, 420.3 (41) $(M + H)^+$; m/e calcd for $C_{26}H_{34}NO_2Si^+$ 420.2354, found 420.2349.



11

Ynamide **11** was prepared from **S2** (1.95 g, 4.6 mmol) following general deprotection procedure. Deprotection reaction gave **11** (1.12 g, 4.3 mmol) in 92% yield.

R_f = 0.26 [20% EtOAc in hexanes]; mp 118-119 °C; $[\alpha]_D^{20}$ = - 121.1 (*c* 1.11, CH_2Cl_2); IR (film) cm^{-1} 3285(w), 2154(w), 1760(s), 1497(w), 1452(w), 1370(m); ^1H NMR (400 MHz, $CDCl_3$) δ 2.75 (s, 1 H), 5.36 (d, 1 H, *J* = 8.0 Hz), 5.95 (d, 1 H, *J* = 8.0 Hz), 6.90-6.94 (m, 4 H), 7.10-7.17 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 61.2, 66.9, 72.4, 81.3, 126.3, 127.6, 128.3, 128.6, 128.8, 129.0, 132.6, 133.4, 156.4; mass spectrum (ESI): m/e (% relative intensity) 286.1 (100) $(M + Na)^+$; m/e calcd for $C_{17}H_{13}NO_2Na^+$ 286.0844, found 286.0857.

A General Procedure for Preparations of Nitrones.[3]

To a mixture of nitroarene (10.0 mmol), aldehyde (10.0 mmol), ammonium chloride (13.0 mmol) in EtOH (20 mL) and H_2O (10 mL) was added Zn powder (20.0 mmol) slowly over 30 min at 0 °C. The mixture was then warmed up to rt and stirred overnight. The reaction mixture was filtered through Celite and exacted by CH_2Cl_2. The combined organic extracts were concentrated *in vacuo*, and the crude products were purified by silica gel flash column chromatography or recrystallization to afford the desired nitrones.

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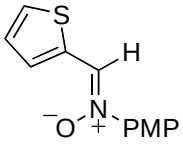
3. Lo, M. M.-C.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 4572.

CHARACTERIZATIONS.



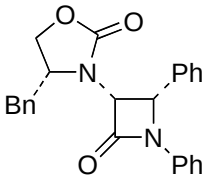
Above nitrone was prepared from the corresponding aldehyde (1.122 g, 10 mmol) and p-nitroanisole (1.531 g, 10 mmol) following general procedure. Reaction gave nitrone (903 mg, 3.87 mmol) in 39% yield.

R_f = 0.14 [40% EtOAc in hexanes]; mp 99-100 °C; IR (film) cm^{-1} 3062(w), 1594(m), 1557(w), 1495(s), 1460(m), 1414(m), 1373(m); ^1H NMR (400 MHz, $CDCl_3$) δ 3.86 (s, 3 H), 6.96 (d, 2 H, *J* = 9.2 Hz), 7.21 (dd, 1 H, *J* = 4.0, 5.2 Hz), 7.54 (dt, 1 H, *J* = 0.8, 5.2 Hz), 7.58 (dt, 1 H, *J* = 0.4, 4.0 Hz), 7.78 (d, 2 H, *J* = 9.2 Hz), 8.42 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.9, 114.4, 122.5, 127.1, 128.1, 129.9, 130.7, 133.5, 140.1, 160.8; mass spectrum (APCI): m/e (% relative intensity) 234.1 (100) $(M + H)^+$.

A General Procedure for Syntheses of β-Lactams Using Ynamide 7.

To a mixture of ynamide **7** (61.0 mg, 0.325 mmol, 1.3 equiv), CuI (10.0 mg, 0.050 mmol, 0.2 equiv), Cy_2NMe (0.23 mL, 1.00 mmol, 4.0 equiv) in CH_3CN (1.5 mL: concd = 0.2 *mM*) was added *N*-phenyl-α-2-(*E*)-phenylethenylnitrone (56.0 mg, 0.25 mmol) in once. The resulting mixture was stirred at 0 °C and was allowed to warm up to rt in ice bath very slowly over 24 h. After TLC showed all the starting nitrone was consumed, the crude mixture was then filtered through a short pad of Celite™ to remove the copper salt. The filtrate was evaporated under reduced pressure to give the crude β-lactam that was purified via silica gel column flash chromatography [isocratic eluent: EtOAc:hexane:CH_2Cl_2 = 3.5:10:10] to afford β-lactam *cis*-**17** (74.0 mg, 0.18 mmol) in 72% yield.

CHARACTERIZATIONS.

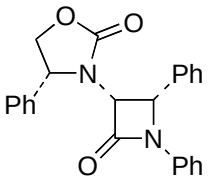


cis-**6a**

Ynamide **5** (131.0 mg, 0.65 mmol, 1.3 equiv), CuCl (10.0 mg, 0.10 mmol, 0.2 equiv), Cy_2NMe (0.46 ml, 2.00 mmol, 4.0 equiv) was dissolved in CH_3CN (3 ml) and stirred at room temperature, *N*-phenyl-α-phenylnitrone (99.0 mg, 0.50 mmol, 1.0 equiv) was added in once. The mixture was stirred at room temperature for 24 hours. After the consumption of ynamide as indicated by TLC, the crude mixture was filtered through a short pad of Celite to remove the copper salt. The filtrate was evaporated under reduced pressure to

give the crude β-lactam that was purified via silica gel column flash chromatography to afford lactam *cis*-**6a** (145.1 mg, 0.36 mmol) in 73% yield.

R_f = 0.25 [33% EtOAc in hexanes]; mp 218-219 °C; $[\alpha]_D^{20}$ = + 47.1 (*c* 0.40, CH_2Cl_2); IR (film) cm^{-1} 2360(m), 1743(s), 1597(m), 1498(m), 1452(w), 1433(m), 1381(m), 1263(m), 1167 (m), 1121(m); ^1H NMR (400 MHz, $CDCl_3$) δ 1.62 (dd, 1 H, *J* = 10.8, 13.2 Hz), 2.80 (dd, 1 H, *J* = 4.4, 13.2 Hz), 3.65 (dd, 1 H, *J* = 6.4, 8.8 Hz), 3.84 (dd, 1 H, *J* = 8.8, 8.8 Hz), 4.06-4.14 (m, 1 H), 5.21 (d, 1 H, *J* = 5.6 Hz), 5.37 (d, 1 H, *J* = 5.6 Hz), 6.96 (d, 2 H, *J* = 8.4 Hz), 7.08 (dd, 1 H, *J* = 7.2, 7.2 Hz), 7.13-7.32 (m, 10 H), 7.39 (dd, 2 H, *J* = 1.0, 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.8, 55.7, 60.9, 63.6, 68.3, 117.6, 125.1, 127.5, 127.7, 128.7, 128.9, 129.1, 129.2, 129.6, 133.3, 135.4, 137.7, 158.1, 161.3; mass spectrum (APCI): m/e (% relative intensity) 399.2 (100) $(M + H)^+$.

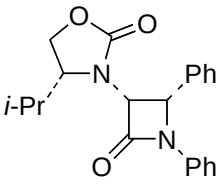


cis-**12**

Ynamide **7** (131.0 mg, 0.65 mmol, 1.3 equiv), CuCl (10.0 mg, 0.10 mmol, 0.2 equiv), Cy_2NMe (0.46 ml, 2.00 mmol, 4.0 equiv) was dissolved in CH_3CN (3 ml) and stirred at room temperature, *N*-phenyl-α-phenylnitrone (99.0 mg, 0.50 mmol, 1.00 equiv) was added in once. The mixture was stirred at room temperature for 24 hours. After the consumption of ynamide as indicated by TLC, the crude mixture was filtered through a short pad of Celite to remove the copper salt. The filtrate was evaporated under reduced

pressure to give the crude β-lactam that was purified via silica gel column flash chromatography to afford lactam *cis*-**12** (152.8 mg, 0.40 mmol) in 80% yield.

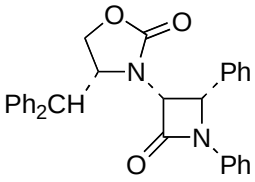
R_f = 0.31 [33% EtOAc in hexanes]; mp > 240 °C; $[\alpha]_D^{20}$ = - 69.9 (*c* 0.83, CH_2Cl_2); IR (film) cm^{-1} 2361(m), 2341(m), 1765(s), 1740(s), 1597(m), 1427(m), 1384(m), 1276(m), 1260(m), 1169(m), 1134 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 3.99 (dd, 1 H, *J* = 7.2, 8.8 Hz), 4.29 (dd, 1 H, *J* = 8.8, 8.8 Hz), 4.61 (dd, 1 H, *J* = 7.2, 8.8 Hz), 4.77 (d, 1 H, *J* = 45.6 Hz), 5.23 (d, 1 H, *J* = 5.6 Hz), 7.07 (td, 1 H, *J* = 1.2, 7.2 Hz), 7.13-7.17 (m, 2 H), 7.21-7.28 (m, 4 H), 7.30-7.34 (m, 8 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 59.8, 61.4, 63.1, 70.8, 117.5, 124.7, 127.7, 127.8, 128.7, 129.0, 129.3, 129.4, 129.7, 132.7, 137.0, 137.5, 157.4, 160.9; mass spectrum (APCI): m/e (% relative intensity) 385.2 (100) $(M + H)^+$.



cis-**13**

Ynamide **8** (50.0 mg, 0.325 mmol, 1.3 equiv), CuCl (5.0 mg, 0.050 mmol, 0.2 equiv), Cy_2NMe (0.23 ml, 1.00 mmol, 4.0 equiv) was dissolved in CH_3CN (1.5 ml) and stirred at room temperature, *N*-phenyl-α-phenylnitrone (49.0 mg, 0.25 mmol, 1.00 equiv) was added in once. The mixture was stirred at room temperature for 24 hours. After the consumption of ynamide as indicated by TLC, the crude mixture was filtered through a short pad of Celite to remove the copper salt. The filtrate was evaporated under reduced pressure to give the crude β-lactam that was purified via silica gel column flash chromatography to afford lactam *cis*-**13** (31.7 mg, 0.09 mmol) in 36% yield.

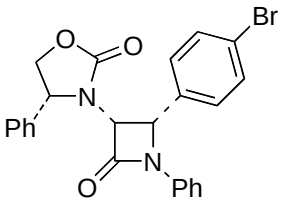
R_f = 0.06 [CH_2Cl_2]; mp 280-283 °C; $[\alpha]_D^{20}$ = 5.30 (*c* 1.075, CH_2Cl_2); IR (film) cm^{-1} 3735(w), 3629(w), 3062(w), 2961(w), 2361(s), 2341(m), 1746(s), 1600(m), 1497(m), 1387(m); ^1H NMR (400 MHz, $CDCl_3$) δ 0.35 (d, 3H, *J* = 6.4 Hz), 0.80 (d, 3H, *J* = 6.8 Hz), 1.73 (dseptet, 1H, *J* = 6.8, 3.2 Hz), 3.74 (ddd, 1H, *J* = 8.4, 4.8, 3.2 Hz), 3.90 (t, 1H, *J* = 8.8 Hz), 3.96 (dd, 1H, *J* = 8.0, 4.0 Hz), 5.07 (d, 1H, *J* = 5.6 Hz), 5.39 (d, 1H, *J* = 5.2 Hz), 7.13 (t, 1H, *J* = 7.6 Hz), 7.30-7.42 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.5, 18.3, 29.5, 59.0, 61.5, 63.6, 63.8, 117.6, 124.9, 127.7, 128.8, 129.1, 129.4, 133.0, 137.6, 158.1, 161.3; mass spectrum (APCI): m/e (% relative intensity) 351.2 (100) $(M + H)^+$.



cis-**14**

Ynamide **9** (50.0 mg, 0.18 mmol, 1.3 equiv), CuI (6.0 mg, 0.03 mmol, 0.2 equiv), Cy_2NMe (0.13 ml, 0.60 mmol, 4.0 equiv) was dissolved in CH_3CN (2.0 ml) and stirred at 0 °C, *N*-phenyl-α-phenylnitrone (30.0 mg, 0.15 mmol, 1.0 equiv) was added in once. The mixture was stirred at 0 °C and was allowed to warm up to rt in ice bath very slowly over 24 hours. After the consumption of ynamide as indicated by TLC, the crude mixture was filtered through a short pad of Celite to remove the copper salt. The filtrate was evaporated under reduced pressure to give the crude β-lactam that was purified via silica gel column flash chromatography to afford lactam *cis*-**14** (19.0 mg, 0.04 mmol) in 28% yield.

R_f = 0.22 [hexane:CH_2Cl_2:EtOAc = 10:10:2]; $[\alpha]_D^{20}$ = - 10.0 (*c* 0.10, CH_2Cl_2); mp > 300 °C; IR (film) cm^{-1} 1760(s), 1749(s), 1600(w), 1493(w), 1429(w), 1387(m);^{1}H NMR (400 MHz, CD_2Cl_2) δ 3.46-3.50 (m, 1H), 3.71-3.74 (m, 1H), 3.99 (d, 1H, *J* = 5.2 Hz), 4.11-4.13 (m, 2 H), 4.90 (d, 1H, *J* = 5.2 Hz), 7.05-7.46 (m, 20H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 55.7, 58.9, 62.2, 64.6, 67.4, 117.5, 124.7, 128.0, 128.36, 128.45, 128.7, 129.2, 129.3, 129.6, 129.7, 130.0, 133.2, 128.1, 140.3, 141.1, 157.2, 161.4, (one aromatic carbon is missing due to overlap); mass spectrum (APCI): m/e (% relative intensity) 475.2 (100) $(M + H)^+$.

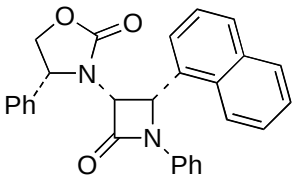


cis-**15**

Ynamide **7** (131.0 mg, 0.65 mmol, 1.3 equiv), CuCl (10.0 mg, 0.10 mmol, 0.2 equiv), Cy_2NMe (0.46 ml, 2.00 mmol, 4.0 equiv) was dissolved in CH_3CN (3 ml) and stirred at room temperature, *N*-phenyl-α-(4-bromophenyl)nitrone (138.0 mg, 0.50 mmol, 1.00 equiv) was added in once. The mixture was stirred at room temperature for 24 hours. After the consumption of ynamide as indicated by TLC, the crude mixture was filtered through a short pad of Celite to remove the copper salt. The filtrate was evaporated under reduced pressure to give the crude β-lactam that was purified via silica gel column flash chromatography to afford lactam *cis*-**15** (88.7 mg, 0.19 mmol) in 77% yield.

R_f = 0.33 [33% EtOAc in hexanes]; mp > 240 °C; $[\alpha]_D^{20}$ = - 74.5 (*c* 0.68, CH_2Cl_2); IR (film) cm^{-1} 2360(m), 2341(m), 1765(s), 1738(s), 1549(m), 1383(m), 1276(m), 1260(m),

1169(m), 1134(m); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.08 (dd, 1 H, *J* = 7.0, 9.0 Hz), 4.46 (dd, 1 H, *J* = 9.0, 9.0 Hz), 4.77 (dd, 1 H, *J* = 7.0, 9.0 Hz), 4.93 (d, 1 H, *J* = 5.5 Hz), 5.20 (d, 1 H, *J* = 5.5 Hz), 6.97 (d, 2 H, *J* = 8.0 Hz), 7.07-7.11 (m, 3 H), 7.26-7.33 (m, 7 H), 7.37 (d, 2 H, *J* = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 59.5, 60.8, 63.3, 71.2, 117.5, 122.7, 125.0, 127.8, 129.2, 129.4, 129.5, 129.7, 131.9, 132.3, 137.3, 137.4, 157.8, 160.8; mass spectrum (APCI): m/e (% relative intensity) 465.0 (95) $(M + H + 2)^+$, 463.0 (100) $(M + H)^+$.

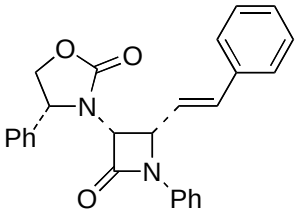


cis-**16**

Ynamide **7** (61.0 mg, 0.325 mmol, 1.3 equiv), CuCl (5.0 mg, 0.050 mmol, 0.2 equiv), Cy_2NMe (0.23 ml, 1.00 mmol, 4.0 equiv) was dissolved in CH_3CN (1.5 ml) and stirred at room temperature, *N*-phenyl-α-(1-naphthyl)nitrone (62.0 mg, 0.25 mmol, 1.0 equiv) was added in once. The mixture was stirred at room temperature for 24 hours. After the consumption of ynamide as indicated by TLC, the crude mixture was filtered through a short pad of Celite to remove the copper salt. The filtrate was evaporated under reduced pressure to give the crude β-lactam that was purified via silica gel column flash chromatography to afford lactam *cis*-**16** (76.7 mg, 0.18 mmol) in 71% yield.

R_f = 0.32 [33% EtOAc in hexanes]; mp > 240 °C; $[\alpha]_D^{20}$ = - 9.14 (*c* 1.03, CH_2Cl_2); IR (film) cm^{-1} 2924(m), 2853(w), 2361(m), 2341(m), 1753(s), 1657(m), 1598(m), 1496(s), 1458(w), 1387(s), 1275(m), 1261(m), 1162(m), 1130(m), 1081(m), 1035(m); ^{1}H NMR

(400 MHz, $CDCl_3$) δ 3.76 (dd, 1 H, *J* = 7.6, 8.8 Hz), 3.89 (dd, 1 H, *J* = 8.8, 8.8 Hz), 4.23 (dd, 1 H, *J* = 7.6, 8.8 Hz), 4.92 (d, 1 H, *J* = 5.2 Hz), 5.86 (d, 1 H, *J* = 5.2 Hz), 7.06-7.13 (m, 3 H), 7.25-7.42 (m, 9 H), 7.62 (dd, 1 H, *J* = 7.2, 8.0 Hz), 7.67-7.72 (m, 1 H), 7.83 (d, 1 H, *J* = 8.0 Hz), 7.98 (t, 2 H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 59.7, 60.1, 63.2, 70.4, 117.7, 122.3, 124.6, 126.2, 126.3, 126.8, 127.0, 127.2, 127.7, 129.0, 129.3, 129.6, 129.7, 129.8, 130.8, 133.8, 136.7, 137.7, 156.9, 161.6; mass spectrum (APCI): m/e (% relative intensity) 435.1 (100) $(M + H)^+$.

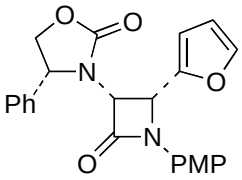


cis-**17**

Ynamide **7** (61.0 mg, 0.325 mmol, 1.3 equiv), CuI (10.0 mg, 0.050 mmol, 0.2 equiv), Cy_2NMe (0.23 ml, 1.00 mmol, 4.0 equiv) was dissolved in CH_3CN (1.5 ml) and stirred at 0 °C, *N*-phenyl-α-2-(*E*)-phenylethenylnitrone (56.0 mg, 0.25 mmol, 1.0 equiv) was added in once. The mixture was stirred at 0 °C and was allowed to warm up to rt in ice bath very slowly over 24 hours. After the consumption of ynamide as indicated by TLC, the crude mixture was filtered through a short pad of Celite to remove the copper salt. The filtrate was evaporated under reduced pressure to give the crude β-lactam that was purified via silica gel column flash chromatography to afford lactam *cis*-**17** (74.0 mg, 0.18 mmol) in 72% yield.

R_f = 0.55 [50% EtOAc in hexanes]; mp 228-229 °C; $[\alpha]_D^{20}$ = - 133.6 (*c* 1.03, CH_2Cl_2); IR (film) cm^{-1} 2971(m), 1738(s), 1426(w), 1366(m); ^1H NMR (400 MHz, $CDCl_3$) δ 4.22 (dd,

1 H, *J* = 6.8, 8.8 Hz), 4.65 (t, 1 H, *J* = 8.8 Hz), 4.71 (d, 1 H, *J* = 5.2 Hz), 4.83 (ddd, 1 H, *J* = 0.8, 5.2, 8.4 Hz), 4.96 (dd, 1 H, *J* = 6.8, 8.8 Hz), 6.08 (dd, 1 H, *J* = 8.4, 15.8 Hz), 6.78 (d, 1 H, *J* = 15.8 Hz), 7.05-7.09 (m, 1H), 7.25-7.41 (m, 14 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 60.3, 61.3, 62.5, 71.2, 117.4, 123.8, 124.7, 127.2, 128.1, 128.9, 129.0, 129.4, 129.8, 135.9, 137.2, 137.4, 137.9, 158.0, 161.2, (one aromatic carbon is missing due to overlap); mass spectrum (APCI): m/e (% relative intensity) 411.2 (100) $(M + H)^+$.

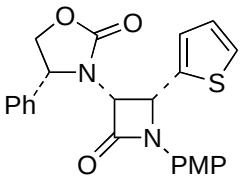


cis-**18**

Ynamide **7** (61.0 mg, 0.325 mmol, 1.3 equiv), CuI (10.0 mg, 0.050 mmol, 0.2 equiv), Cy_2NMe (0.23 ml, 1.00 mmol, 4.0 equiv) was dissolved in CH_3CN (1.5 ml) and stirred at 0 °C, *N*-(4-methoxyphenyl)-α-(2-furyl)nitrone (54.0 mg, 0.25 mmol, 1.00 equiv) was added in once. The mixture was stirred at 0 °C and was allowed to warm up to rt in ice bath very slowly over 24 hours. After the consumption of ynamide as indicated by TLC, the crude mixture was filtered through a short pad of Celite to remove the copper salt. The filtrate was evaporated under reduced pressure to give the crude β-lactam that was purified via silica gel column flash chromatography to afford lactam *cis*-**18** (61.9 mg, 0.15 mmol) in 61% yield.

R_f = 0.42 [50% EtOAc in hexanes]; mp 207-208 °C; $[\alpha]_D^{20}$ = - 75.5 (*c* 0.42, CH_2Cl_2); IR (film) cm^{-1} 1750(s), 1512(s), 1469(w), 1421(m), 1394(w); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.76 (s, 3 H), 4.07 (t, 1 H, *J* = 8.5 Hz), 4.43 (t, 1 H, *J* = 8.5 Hz), 4.53 (t, 1 H, *J* = 8.5 Hz), 4.57 (d, 1 H, *J* = 5.0 Hz), 5.18 (d, 1 H, *J* = 5.0 Hz), 6.36-6.40 (m, 2H), 6.81 (d, 2 H, *J* =

8.0 Hz), 7.28 (d, 2 H, *J* = 8.0 Hz), 7.32-7.34 (m, 2 H), 7.37-7.43 (m, 3 H), 7.48 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.6, 55.7, 60.3, 62.9, 70.6, 111.7, 111.8, 114.5, 118.9, 127.8, 129.75, 129.77, 130.7, 136.8, 143.3, 147.3, 156.8, 157.1, 160.1; mass spectrum (APCI): m/e (% relative intensity) 405.1 (100) $(M + H)^+$.

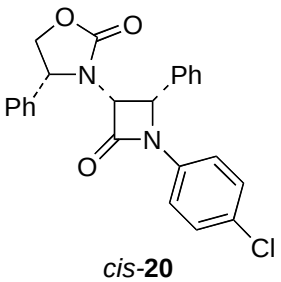


cis-**19**

Ynamide **7** (61.0 mg, 0.325 mmol, 1.3 equiv), CuI (10.0 mg, 0.050 mmol, 0.2 equiv), Cy_2NMe (0.23 ml, 1.00 mmol, 4.0 equiv) was dissolved in CH_3CN (1.5 ml) and stirred at 0 °C, *N*-(4-methoxyphenyl)-α-(2-thienyl)nitrone (58.0 mg, 0.25 mmol, 1.0 equiv) was added in once. The mixture was stirred at 0 °C and was allowed to warm up to rt in ice bath very slowly over 24 hours. After the consumption of ynamide as indicated by TLC, the crude mixture was filtered through a short pad of Celite to remove the copper salt. The filtrate was evaporated under reduced pressure to give the crude β-lactam that was purified via silica gel column flash chromatography to afford lactam *cis*-**19** (63.0 mg, 0.15 mmol) in 60% yield.

R_f = 0.19 [40% EtOAc in hexanes]; mp 229-231 °C; $[\alpha]_D^{20}$ = - 58.2 (*c* 0.82, CH_2Cl_2); IR (film) cm^{-1} 1744(s), 1512(m), 1467(w), 1428(m), 1388(w); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.74 (s, 3 H), 4.05 (dd, 1 H, *J* = 7.0, 9.0 Hz), 4.39 (dd, 1 H, *J* = 9.0, 9.0 Hz), 4.63-4.67 (m, 2 H), 5.35 (d, 1 H, *J* = 5.0 Hz), 6.79 (d, 2 H, *J* = 8.5 Hz), 6.96-6.98 (m, 2 H), 7.24-7.25 (m, 2 H), 7.29 (d, 2 H, *J* = 8.5 Hz), 7.32 (dd, 1 H, *J* = 1.5, 5.0 Hz), 7.35-7.39 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.7, 57.5, 60.1, 63.5, 70.8, 114.6, 119.0, 126.4,

127.8, 128.2, 128.5, 129.6, 129.7, 130.8, 135.3, 137.0, 156.8, 157.3, 160.1; mass spectrum (APCI): m/e (% relative intensity) 421.1 (100) $(M + H)^+$.

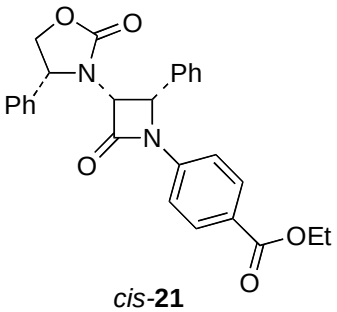


cis-**20**

Ynamide **7** (61.0 mg, 0.325 mmol, 1.3 equiv), CuCl (5.0 mg, 0.050 mmol, 0.2 equiv), Cy_2NMe (0.23 ml, 1.00 mmol, 4.0 equiv) was dissolved in CH_3CN (1.5 ml) and stirred at room temperature, *N*-(4-chlorophenyl)-α-phenylnitrone (58.0 mg, 0.25 mmol, 1.0 equiv) was added in once. The mixture was stirred at room temperature for 24 hours. After the consumption of ynamide as indicated by TLC, the crude mixture was filtered through a short pad of Celite to remove the copper salt. The filtrate was evaporated under reduced pressure to give the crude β-lactam that was purified via silica gel column flash chromatography to afford lactam *cis*-**20** (67.8 mg, 0.16 mmol) in 65% yield.

R_f = 0.28 [EtOAc in hexanes]; mp > 240 °C; $[\alpha]_D^{20}$ = - 69.0 (*c* 1.29, CH_2Cl_2); IR (film) cm^{-1} 2361(m), 2341(m), 1743(s), 1597(m), 1495(s), 1422(m), 1388(s), 1276(m), 1261(m), 1168(m), 1124(m), 1093(m), 1040(m); ^1H NMR (400 MHz, $CDCl_3$) δ 3.98 (dd, 1 H, *J* = 7.6, 7.6 Hz), 4.27 (dd, 1 H, *J* = 7.6, 7.6 Hz), 4.55 (dd, 1 H, *J* = 7.6, 7.6 Hz), 4.71 (d, 1 H, *J* = 4.0 Hz), 5.19 (d, 1 H, *J* = 4.0 Hz), 7.15-7.27 (m, 8 H), 7.32-7.37 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 59.9, 61.6, 63.2, 70.7, 118.7, 127.3, 127.7, 127.8,

128.9, 129.1, 129.4, 129.6, 129.7, 132.3, 136.0, 136.8, 157.2, 160.8; mass spectrum (APCI): m/e (% relative intensity) 419.2 (35) $(M + H + 2)^+$, 417.2 (100) $(M + H)^+$.

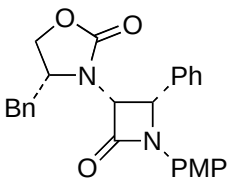


cis-**21**

Ynamide **7** (61.0 mg, 0.325 mmol, 1.3 equiv), CuCl (5.0 mg, 0.050 mmol, 0.2 equiv), Cy_2NMe (0.23 ml, 1.00 mmol, 4.0 equiv) was dissolved in CH_3CN (1.5 ml) and stirred at room temperature, *N*-(4-carboethoxyphenyl)-α-phenylnitrone (67.0 mg, 0.25 mmol, 1.0 equiv) was added in once. The mixture was stirred at room temperature for 24 hours. After the consumption of ynamide as indicated by TLC, the crude mixture was filtered through a short pad of Celite to remove the copper salt. The filtrate was evaporated under reduced pressure to give the crude β-lactam that was purified via silica gel column flash chromatography to afford lactam *cis*-**21** (71.5 mg, 0.16 mmol) in 63% yield.

R_f = 0.22 [33% EtOAc in hexanes]; mp > 240 °C; $[\alpha]_D^{20}$ = - 30.8 (*c* 0.37, CH_2Cl_2); IR (film) cm^{-1} 2990(w), 2361(m), 2341(m), 1762(s), 1705(m), 1605(m), 1426(m), 1386(m), 1276(s), 1262(s), 1042(w); ^1H NMR (400 MHz, $CDCl_3$) δ 1.35 (t, 3 H, 3.98, *J* = 7.2 Hz), 4.00 (dd, 1 H, *J* = 8.0, 8.0 Hz), 4.27-4.36 (m, 3 H), 4.57 (dd, 1 H, *J* = 8.0, 8.0 Hz), 4.76 (d, 1 H, *J* = 5.2 Hz), 5.26 (d, 1 H, *J* = 5.2 Hz), 7.16-7.20 (m, 2 H), 7.23-7.27 (m, 2 H), 7.32-7.38 (m, 8 H), 7.95 (d, 2 H, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6, 59.9, 61.1, 61.7, 63.2, 70.8, 117.1, 126.5, 127.7, 127.8, 129.0, 129.2, 129.6, 129.7, 131.1,

132.1, 136.7, 141.0, 157.2, 161.2, 166.1; mass spectrum (APCI): m/e (% relative intensity) 457.1 (100) $(M + H)^+$.

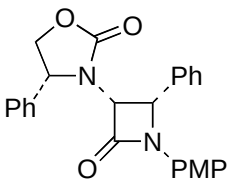


cis-**22**

Ynamide **5** (131.0 mg, 0.65 mmol, 1.3 equiv), CuCl (10.0 mg, 0.10 mmol, 0.2 equiv), Cy_2NMe (0.46 ml, 2.00 mmol, 4.0 equiv) was dissolved in CH_3CN (3 ml) and stirred at room temperature, *N*-(4-methoxyphenyl)-α-phenylnitrone (114.0 mg, 0.50 mmol, 1.0 equiv) was added in once. The mixture was stirred at room temperature for 24 hours. After the consumption of ynamide as indicated by TLC, the crude mixture was filtered through a short pad of Celite to remove the copper salt. The filtrate was evaporated under reduced pressure to give the crude β-lactam that was purified via silica gel column flash chromatography to afford lactam *cis*-**22** (125.4 mg, 0.29 mmol) in 59% yield.

R_f = 0.51 [50% EtOAc in hexanes]; mp 173-176 °C; $[\alpha]_D^{20}$ = + 48.8 (*c* 0.45, CH_2Cl_2); IR (film) cm^{-1} 1738(s), 1514(m), 1427(w), 1391(w); ^1H NMR (400 MHz, $CDCl_3$) δ 1.68 (dd, 1 H, *J* = 10.8, 13.2 Hz), 2.87 (dd, 1 H, *J* = 4.0, 13.2 Hz), 3.72 (dd, 1 H, *J* = 6.4, 8.8 Hz), 3.79 (s, 3 H), 3.92 (dd, 1 H, *J* = 8.8, 8.8 Hz), 4.16-4.23 (m, 1 H), 5.27 (d, 1 H, *J* = 5.4 Hz), 5.40 (d, 1 H, *J* = 5.4 Hz), 6.87 (d, 2 H, *J* = 9.2 Hz), 7.03 (d, 2 H, *J* = 6.8 Hz), 7.20-7.31 (m, 5 H), 7.34-7.42 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.8, 55.7, 55.7, 60.9, 63.6, 68.3, 114.8, 118.9, 127.5, 127.7, 128.7, 128.9, 129.1, 131.2, 133.5, 135.5, 156.9,

158.2, 160.7, (one aromatic carbon is missing due to overlap); mass spectrum (APCI): m/e (% relative intensity) 429.2 (100) $(M + H)^+$.

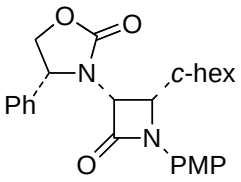


cis-**23**

Ynamide **7** (61.0 mg, 0.325 mmol, 1.3 equiv), CuCl (5.0 mg, 0.050 mmol, 0.2 equiv), Cy_2NMe (0.23 ml, 1.00 mmol, 4.0 equiv) was dissolved in CH_3CN (1.5 ml) and stirred at room temperature, *N*-(4-methoxyphenyl)-α-phenylnitrone (57.0 mg, 0.25 mmol, 1.0 equiv) was added in once. The mixture was stirred at room temperature for 24 hours. After the consumption of ynamide as indicated by TLC, the crude mixture was filtered through a short pad of Celite to remove the copper salt. The filtrate was evaporated under reduced pressure to give the crude β-lactam that was purified via silica gel column flash chromatography to afford lactam *cis*-**23** (62.0 mg, 0.15 mmol) in 60% yield.

R_f = 0.19 [33% EtOAc in hexanes]; mp > 240 °C; $[\alpha]_D^{20}$ = - 1.28 (*c* 1.33, CH_2Cl_2); IR (film) cm^{-1} 2925(w), 2853(m), 2360(w), 1751(s), 1656(w), 1598(m), 1496(m), 1457(m), 1388(s), 1263(m), 1163 (m), 1036(m); ^1H NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 3 H), 3.99 (dd, 1 H, *J* = 7.2, 8.8 Hz), 4.31 (dd, 1 H, *J* = 8.8, 8.8 Hz), 4.62 (dd, 1 H, *J* = 7.2, 8.8 Hz), 4.78 (d, 1 H, *J* = 4.8 Hz), 5.19 (d, 1 H, *J* = 4.8 Hz), 6.79 (d, 2 H, *J* = 9.2 Hz), 7.12-7.15 (m, 2 H), 7.18-7.22 (m, 2 H), 7.24-7.27 (m, 2 H), 7.30-7.33 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.7, 59.8, 61.4, 63.1, 70.8, 114.5, 118.8, 127.7, 127.8, 128.6, 129.0,

129.4, 129.6, 131.1, 132.9, 137.1, 156.6, 157.4, 160.3; mass spectrum (APCI): m/e (% relative intensity) 415.1 (100) $(M + H)^+$.

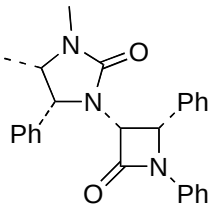


cis-**24**

Ynamide **7** (61.0 mg, 0.325 mmol, 1.3 equiv), CuI (10.0 mg, 0.050 mmol, 0.2 equiv), Cy_2NMe (0.23 ml, 1.00 mmol, 4.0 equiv) was dissolved in CH_3CN (1.5 ml) and stirred at 0 °C, *N*-(4-methoxyphenyl)-α-cyclohexylnitrone (58.0 mg, 0.25 mmol, 1.0 equiv) was added in once. The mixture was stirred at 0 °C and was allowed to warm up to rt in ice bath very slowly over 24 hours. After the consumption of ynamide as indicated by TLC, the crude mixture was filtered through a short pad of Celite to remove the copper salt. The filtrate was evaporated under reduced pressure to give the crude β-lactam that was purified via silica gel column flash chromatography to afford lactam *cis*-**24** (61.2 mg, 0.15 mmol) in 60% yield.

R_f = 0.49 [50% EtOAc in hexanes]; mp 204-206 °C; $[\alpha]_D^{20}$ = - 122.6 (*c* 1.05, CH_2Cl_2); IR (film) cm^{-1} 2923(m), 2851(m), 1759(m), 1742(s), 1511(s), 1458(w), 1423(m), 1388(m), 1356(w); ^1H NMR (400 MHz, $CDCl_3$) δ 0.78-0.85 (m, 2 H), 0.87-0.94 (m, 1 H), 0.99-1.10 (m, 2 H), 1.13-1.26 (m, 2 H),1.44-1.45 (m, 1 H), 1.56-1.59 (m, 1 H), 1.64-1.70 (m, 2 H), 3.77 (s, 3 H), 3.87 (dd, 1 H, *J* = 5.2, 10.0 Hz), 4.45 (dd, 1 H, *J* = 6.0, 9.2 Hz), 4.78 (dd, 1 H, *J* = 9.2, 9.2 Hz), 4.88 (br, 1 H), 5.25-5.29 (m, 1 H), 6.83 (d, 2 H, *J* = 9.0 Hz), 7.18 (d, 2 H, *J* = 9.0 Hz), 7.36-7.39 (m, 1 H), 7.42-7.50 (m, 4 H); ^{13}C NMR (125 MHz,

$CDCl_3$) δ 25.5, 25.9, 26.3, 29.7, 31.7, 38.8, 55.7, 59.5, 61.9, 63.5, 70.8, 114.3, 121.0, 128.7, 129.7, 129.8, 131.2, 138.9, 157.1, 158.6, 162.8; mass spectrum (APCI): m/e (% relative intensity) 421.2 (100) $(M + H)^+$.

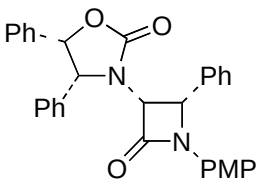


cis-**25**

Ynamide **10** (139.0 mg, 0.65 mmol, 1.3 equiv), CuCl (10.0 mg, 0.10 mmol, 0.2 equiv), Cy_2NMe (0.46 ml, 2.00 mmol, 4.0 equiv) was dissolved in CH_3CN (3 ml) and stirred at room temperature, *N*-phenyl-α-phenylnitrone (99.0 mg, 0.50 mmol, 1.0 equiv) was added in once. The mixture was stirred at room temperature for 24 hours. After the consumption of ynamide as indicated by TLC, the crude mixture was filtered through a short pad of Celite to remove the copper salt. The filtrate was evaporated under reduced pressure to give the crude β-lactam that was purified via silica gel column flash chromatography to afford lactam *cis*-**25** (125.0 mg, 0.30 mmol) in 61% yield.

R_f = 0.18 [33% EtOAc in hexanes]; mp > 240 °C; $[\alpha]_D^{20}$ = - 61.6 (*c* 0.66, CH_2Cl_2); IR (film) cm^{-1} 2360(m), 1752(s), 1704(s), 1598(m), 1434(m), 1381(m), 1276(m), 1262(m), 1114 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 0.52 (d, 3 H, *J* = 6.4 Hz), 2.42 (s, 3 H), 3.12 (dt, 1 H, *J* = 6.8, 9.2 Hz), 4.26 (d, 1 H, *J* = 9.2 Hz), 4.55 (d, 1 H, *J* = 5.2 Hz), 5.09 (d, 1 H, *J* = 5.2 Hz), 6.97 (tt, 1 H, *J* = 1.2, 7.2 Hz), 7.07 (dd, 2 H, *J* = 2.4, 8.0 Hz), 7.14-7.35 (m, 12 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.2, 28.8, 56.2, 61.9, 62.1, 64.4, 117.5, 124.2, 128.2,

128.3, 128.4, 128.5, 128.6, 128.9, 129.2, 133.7, 135.6, 138.0, 160.1, 162.7; mass spectrum (APCI): m/e (% relative intensity) 412.1 (100) $(M + H)^+$.



cis-**26**

Ynamide **11** (47.0 mg, 0.18 mmol, 1.3 equiv), CuI (6.0 mg, 0.03 mmol, 0.2 equiv), Cy_2NMe (0.13 ml, 0.60 mmol, 4.0 equiv) was dissolved in CH_3CN (2.0 ml) and stirred at 0 °C, *N*-(4-methoxyphenyl)-α-phenylnitrone (34.0 mg, 0.15 mmol, 1.0 equiv) was added in once. The mixture was stirred at 0 °C and was allowed to warm up to rt in ice bath very slowly over 24 hours. After the consumption of ynamide as indicated by TLC, the crude mixture was filtered through a short pad of Celite to remove the copper salt. The filtrate was evaporated under reduced pressure to give the crude β-lactam that was purified via silica gel column flash chromatography to afford lactam *cis*-**26** (44.0 mg, 0.09 mmol) in 60% yield.

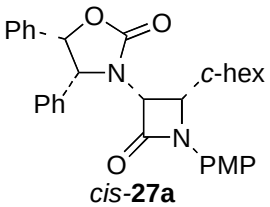
R_f = 0.50 [EtOAc:CH_2Cl_2:hexane=1:2:2]; mp 291-292 °C; $[\alpha]_D^{20}$ = - 18.2 (*c* 0.11, CH_2Cl_2); IR (film) cm^{-1} 3066(w), 1745(s), 1586(w), 1518(m), 1454(w), 1426(w), 1401(m), 1353(w); ^1H NMR (400 MHz, $CDCl_3$) δ 3.76 (s, 3 H), 4.66 (d, 1 H, *J* = 5.2 Hz), 4.71 (d, 1 H, *J* = 8.4 Hz), 5.21-5.23 (m, 2 H), 6.80-6.85 (m, 6 H), 7.02-7.04 (m, 3 H), 7.07-7.09 (m, 3 H), 7.32 (d, 2 H, *J* = 9.2 Hz), 7.40-7.43 (m, 5 H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 56.0, 62.1, 64.3, 65.6, 80.4, 114.8, 119.0, 126.7, 128.2, 128.4, 128.5, 128.6,

129.0, 129.1, 129.26, 129.31, 131.7, 133.7, 134.1, 134.7, 156.8, 157.0, 160.7; mass spectrum (APCI): m/e (% relative intensity) 491.2 (100) $(M + H)^+$.

A Large Scale Preparation of β-Lactam *cis*-27a.

To a mixture of ynamide **11** (1.29 g, 4.90 mmol), CuI (163.0 mg, 0.86 mmol), Cy_2NMe (3.60 mL, 17.1 mmol) in CH_3CN (55 mL) stirring in a -15 ^oC ice/salt bath was added *N*-(4-methoxyphenyl)-α-cyclohexylnitrone (994.0 mg, 4.27 mmol) in once. The mixture was stirred at –15 °C and was allowed to warm up to rt in ice/salt bath slowly. After 36 h, TLC showed that the starting nitrone was all consumed. The reaction mixture was filtered through a short pad of Celite^{TM} to remove the copper salt. The solvent was evaporated under reduced pressure to give the crude β-lactam, which was purified via silica gel column flash chromatography [isocratic eluent: hexane:CH_2Cl_2:EtOAc = 10:10:2] to afford β-lactam *cis*-**27a** (1.33 g, 2.70 mmol) in 62% yield and *cis*-**27b** (130 mg, 0.27 mmol) in 6% yield.

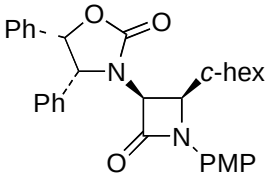
CHARACTERIZATION.



cis-**27a**

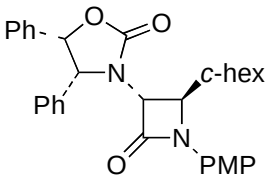
R_f = 0.36 [40% EtOAc in hexanes]; mp 261-264 °C; $[\alpha]_D^{20}$ = + 40.6 (*c* 0.12, CH_2Cl_2); IR (film) cm^{-1} 2981(m), 1746(s), 1512(m), 1455(w), 1380(m); ^1H NMR (500 MHz, $CDCl_3$) δ 0.99-1.24 (m, 4 H), 1.31-1.39 (m, 1 H), 1.63-1.73 (m, 3 H), 1.85-1.87 (m, 3 H), 3.82

(s, 3 H), 4.01 (dd, 1 H, *J* = 5.0, 10.0 Hz), 4.57 (d, 1 H, *J* = 5.0 Hz), 5.20 (d, 1 H, *J* = 8.0 Hz), 5.98 (d, 1 H, *J* = 8.0 Hz), 6.88 (d, 2 H, *J* = 8.8 Hz), 7.06-7.17 (m, 10 H), 7.34 (d, 2 H, *J* = 8.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.4, 25.6, 26.1, 30.3, 31.6, 38.9, 55.4, 61.5, 63.2, 66.1, 80.4, 113.9, 120.4, 126.0, 127.9, 128.1, 128.5, 128.6, 131.2, 133.9, 134.0, 156.5, 157.6, 162.6, (one aromatic carbon is missing due to overlap); mass spectrum (APCI): m/e (% relative intensity) 497.2 (100) $(M + H)^+$.



cis-**27b**

R_f = 0.28 [40% EtOAc in hexanes]; mp 196-198 °C; $[\alpha]_D^{20}$ = - 64.6 (*c* 0.96, CH_2Cl_2); IR (film) cm^{-1} 3036(w), 2929(w), 2852(w), 1742(s), 1512(m), 1455(w), 1412(w), 1374(m); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.07-1.37 (m, 5 H), 1.71-1.83 (m, 5 H), 1.99-2.05 (m, 1 H), 3.76 (s, 3 H), 4.13 (dd, 1 H, *J* = 5.5, 5.5 Hz), 5.03 (d, 1 H, *J* = 5.5 Hz), 5.27 (d, 1 H, *J* = 7.2 Hz), 5.85 (d, 1 H, *J* = 7.2 Hz), 6.81 (d, 2 H, *J* = 9.0 Hz), 6.88-6.90 (m, 2 H), 6.97-6.99 (m, 2 H), 7.10-7.16 (m, 6 H), 7.24 (d, 2 H, *J* = 9.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.1, 26.3, 26.4, 30.2, 31.7, 39.2, 55.4, 60.8, 62.1, 67.1, 81.1, 114.0, 119.9, 126.1, 127.5, 127.9, 128.1, 128.2, 128.4, 131.2, 133.5, 134.0, 156.5, 158.0, 161.1; mass spectrum (APCI): m/e (% relative intensity) 497.2 (100) $(M + H)^+$.



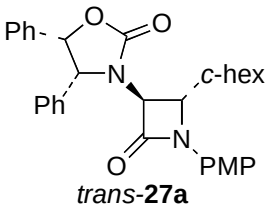
trans-**27b**

R_f = 0.42 [40% EtOAc in hexanes]; mp 93-96 °C; $[\alpha]_D^{20}$ = - 32.1 (*c* 0.52, CH_2Cl_2); IR (film) cm^{-1} 2925(w), 2852(w), 1747(s), 1511(s), 1454(w), 1393(m); ^1H NMR (400 MHz, $CDCl_3$) δ 0.83-1.13 (m, 5 H), 1.42-1.54 (m, 2 H), 1.61-1.70 (m, 4 H), 3.24 (dd, 1 H, *J* = 2.2, 5.2 Hz), 3.76 (s, 3 H), 5.03 (d, 1 H, *J* = 2.2 Hz), 5.13 (d, 1 H, *J* = 8.2 Hz), 6.01 (d, 1 H, *J* = 8.2 Hz), 6.78 (d, 2 H, *J* = 8.6 Hz), 6.92-6.95 (m, 4 H), 7.01-7.12 (m, 8 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.8, 26.0, 26.1, 26.3, 26.5, 38.0, 55.7, 61.5, 62.7, 63.6, 80.3, 114.6, 120.5, 126.1, 128.1, 128.3, 128.7, 129.1, 130.0, 134.4, 135.5, 157.10, 157.15, 162.4 (one aromatic carbon is missing due to overlap); mass spectrum (APCI): m/e (% relative intensity) 497.2 (100) $(M + H)^+$.

Epimerization of *Cis*-27a.

To a solution of *cis*-**27a** (30.0 mg, 0.060 mmol) in toluene (3 mL) was added DBU (46.0 mg, 0.30 mmol). The resulting mixture was refluxed in oil bath under nitrogen for 24-48 h while being monitored with TLC analysis. When the starting material was all consumed, the reaction mixture was cooled to rt and concentrated *in vacuo*. The crude residue was purified by silica gel flash column chromatography to afford *trans*-**27a** (28.8 mg, 0.058 mmol) in 96% yield. The yield of epimerization of *cis*-**27b** to *trans*-**27b** is 96% using the same procedure.

CHARACTERIZATION.



trans-**27a**

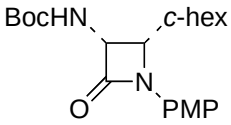
R_f = 0.24 [40% EtOAc in hexanes]; mp 223-224 °C; $[\alpha]_D^{20}$ = - 14.0 (*c* 0.37, CH_2Cl_2); IR (film) cm^{-1} 2922(m), 2852(w), 1742(s), 1731(s), 1514(m), 1452(w), 1417(m); ^1H NMR (400 MHz, $CDCl_3$) δ 0.67-1.15 (m, 5 H), 1.43-1.46 (m, 1 H), 1.52-1.62 (m, 4 H), 1.73-1.80 (m, 1 H), 3.78 (s, 3 H), 4.32 (d, 1 H, *J* = 2.4 Hz), 4.55 (dd, 1 H, *J* = 2.4, 4.4 Hz), 5.24 (d, 1 H, *J* = 8.2 Hz), 5.94 (d, 1 H, *J* = 8.2 Hz), 6.84 (d, 2 H, *J* = 9.2 Hz), 6.94-6.97 (m, 2 H), 6.99-7.01 (m, 2 H), 7.09-7.13 (m, 6 H), 7.23 (d, 2 H, *J* = 9.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.0, 26.27, 26.30, 27.0, 29.2, 38.1, 55.7, 61.1, 62.2, 66.7, 80.2, 114.6, 120.7, 126.2, 128.23, 128.25, 128.6, 128.7, 129.1, 130.5, 134.0, 134.5, 157.1, 157.2, 162.3; mass spectrum (APCI): m/e (% relative intensity) 497.2 (100) $(M + H)^+$.

Hydrogenation of *Cis*-27a.

To a 15 mL glass tube were added β-lactam *cis*-**27a** (400.0 mg, 0.81 mmol), $Pd(OH)_2/C$ (20%, 168.0 mg, 0.24 mmol), $(Boc)_2O$ (528.0 mg, 2.40 mmol) and MeOH (10 mL). The mixture was stirred at room temperature under H_2 (300 *psi*) in a Parr 4790 pressure vessel for 16 h. TLC showed the starting material was consumed, the mixture was filtered through Celite™, and the filtrate was concentrated *in vacuo*. The crude products were purified by silica gel flash column chromatography [isocratic eluent: hexane:CH_2Cl_2:EtOAc = 10:10:3] to afford the desired Boc- and PMP-protected α-amino-β-lactam **28** (289.0 mg, 0.77 mmol) in 96% yield.

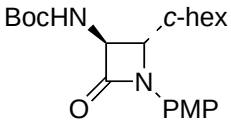
Hydrogenation of *trans*-**27a** was carried using the above procedure to give the Boc- and PMP-protected α-amino-β-lactam **30** in 85% yield.

CHARACTERIZATIONS.



28

R_f = 0.24 [hexane:CH_2Cl_2:EtOAc= 10:10:3]; mp 174-176 °C; $[\alpha]_D^{20}$ = + 1.33 (*c* 0.75, CH_2Cl_2); IR (film) cm^{-1} 3336(w), 2929(w), 2853(w), 1748(m), 1712(m), 1511(s), 1451(w), 1367 (w); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05-1.25 (m, 5 H), 1.44 (s, 9 H), 1.57-1.59 (m, 1 H), 1.66-1.73 (m, 5 H), 3.77 (s, 3 H), 4.02 (dd, 1 H, *J* = 5.5, 7.5 Hz), 5.18 (dd, 1 H, *J* = 5.5, 9.0 Hz), 5.47 (d, 1 H, *J* = 9.0 Hz), 6.83 (d, 2 H, *J* = 9.0 Hz), 7.29 (d, 2 H, *J* = 9.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.8, 26.09, 26.11, 28.2, 29.8, 30.5, 39.4, 55.4, 58.7, 62.5, 80.3, 114.1, 119.8, 131.3, 155.1, 156.5, 165.1; mass spectrum (APCI): m/e (% relative intensity) 375.2 (10) $(M + H)^+$, 319.1 (85), 218.2 (100).



30

R_f = 0.56 [40% EtOAc in hexanes]; mp 67-73 °C; $[\alpha]_D^{20}$ = + 23.8 (*c* 0.83, CH_2Cl_2); IR (film) cm^{-1} 2925(w), 2852(w), 1746(m), 1710(m), 1510(s), 1449(w), 1390(w); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.09-1.29 (m, 5 H), 1.48 (s, 9 H), 1.60-1.62 (m, 1 H), 1.70-1.75 (m, 3 H), 1.81-1.83 (m, 1 H), 2.00 (br, 1 H), 3.81 (s, 3 H), 3.87 (br, 1 H), 4.79 (d, 1 H, *J* = 7.5 Hz), 5.41 (d, 1 H, *J* = 7.5 Hz), 6.88 (d, 2 H, *J* = 8.5 Hz), 7.30 (d, 2 H, *J* = 8.5 Hz); ^{13}C

NMR (125 MHz, $CDCl_3$) δ 26.0, 26.2, 26.3, 26.4, 28.6, 29.2, 37.8, 55.7, 58.7, 66.9, 80.5, 114.7, 120.0, 130.9, 154.9, 156.7, 164.7; mass spectrum (MALDI): m/e (% relative intensity) 397.2 (2) $(M + Na)^+$, 355.2 (100); m/e calcd for $C_{21}H_{30}N_2O_4Na^+$ 397.2098, found 397.2111.

CAN Oxidation of β-Lactam 30.[4]

To a 50 mL flask filled with nitrogen was added the Boc- and PMP-protected α-amino-β-lactam **30** (98.0 mg, 0.26 mmol) and CH_3CN (15 mL). The resulting mixture was cooled to 0 °C, and a solution of CAN (717.0 mg, 1.31 mmol) in H_2O (15 mL) was added dropwise via syringe over 15 min. The reaction progress was monitored with TLC analysis. After about 4 h, the mixture was diluted with H_2O (60 mL), and extracted with EtOAc (3 × 40 mL). The combined EtOAc extracts were washed with sat aq $NaHCO_3$ (40 mL), and the aqueous layer was extracted with additional EtOAc (40 mL). The combine organic extracts were washed with 3 × 30 mL 10% aq $NaHSO_3$ solution until the aqueous layer remained colorless. The organic layer was then washed with 30 mL of sat aq $NaHCO_3$ and 30 mL of sat aq NaCl solution, dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude product. Silica gel flash column chromatography [isocratic eluent: CH_2Cl_2:EtOAc = 2:3] give the desired Boc-protected α-amino-β-lactam **31**(60.0 mg, 0.22 mmol) in 86% yield.

CAN Oxidation of **28** was carried using the above procedure to give the Boc-protected α-amino-β-lactam **29** in 77% yield.

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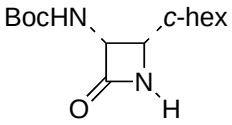
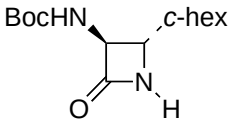
4. Kronenthal. D. R.; Han, C. Y.; Taylor, M. K. *J. Org. Chem.* **1982**, *47*, 2765.

CHARACTERIZATIONS.



29

R_f = 0.22 [CH_2Cl_2:EtOAc =2:1]; mp 70-74 °C; $[\alpha]_D^{20}$ = - 25.8 (*c* 1.00, CH_2Cl_2); IR (film) cm^{-1} 2927(w), 2852(w), 1756(s), 1687(s), 1528(m), 1449(w), 1366(m); ^1H NMR (500 MHz, $CDCl_3$) δ 0.82-0.96 (m, 2 H), 1.13-1.37 (m, 4 H), 1.41 (s, 9 H), 1.57-1.75 (m, 5 H), 3.37 (dd, 1 H, *J* = 4.5, 10.0 Hz), 5.03 (dd, 1 H, *J* = 4.4, 8.6 Hz), 5.43 (d, 1 H, *J* = 9.3 Hz), 6.76 (br, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.1, 25.6, 26.1, 28.2, 29.0, 29.4, 38.3, 59.8, 59.9, 80.2, 155.0, 168.7; mass spectrum (APCI): m/e (% relative intensity) 269.2 (5) $(M + H)^+$, 213.1 (100).



31

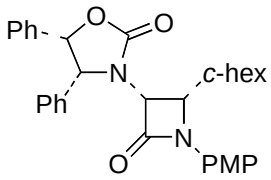
R_f = 0.24 [CH_2Cl_2:EtOAc =3:2]; mp 68-75 °C; $[\alpha]_D^{20}$ = - 22.1 (*c* 3.02, CH_2Cl_2); IR (film) cm^{-1} 3308(m), 2977(w), 2923(m), 2853(w), 1763(s), 1711(s), 1692(s), 1564(w), 1547(m), 1530 (m), 1503(w), 1450(w), 1391(m), 1366(m); ^1H NMR (500 MHz, $CDCl_3$) δ 0.95-1.02 (m, 2 H), 1.14-1.29 (m, 3 H), 1.41-1.44 (m, 10 H), 1.67-1.77 (m, 4 H), 1.85-1.87 (m, 1 H), 3.27 (dd, 1 H, *J* = 2.5, 8.5 Hz), 4.45 (d, 1 H, *J* = 8.0 Hz), 5.37 (d, 1 H, *J* = 8.0 Hz), 6.74 (br, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.7, 25.8, 26.3, 28.6, 28.7, 29.5,

41.6, 62.2, 63.7, 80.5, 155.0, 168.7; mass spectrum (APCI): m/e (% relative intensity) 267.2 (100) $(M - H)^-$.

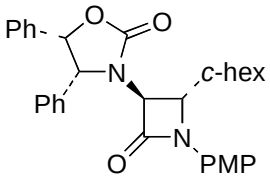
Attempted Epimerization of *cis*-27b Under the Kinugasa Reaction Conditions.

To a flame dried 25 mL flask filled with argon were charged with β-lactam ***cis*-27b** (30.0 mg, 0.060 mmol), CuI (2.30 mg, 0.012 mmol), and CH_3CN (2 mL). The resulting mixture was stirred at 0 °C, and Cy_2NMe (50.0 μL, 0.24 mmol) was added via syringe. The solution was allowed to warm up to rt in ice bath very slowly. After 40 h, the reaction mixture was filtered through a short pad of silica gel [isocratic eluent: CH_2Cl_2:EtOAc = 3:1]. The filtrate was concentrated *in vacuo* and crude ^1H NMR showed no *trans*-**27b**.

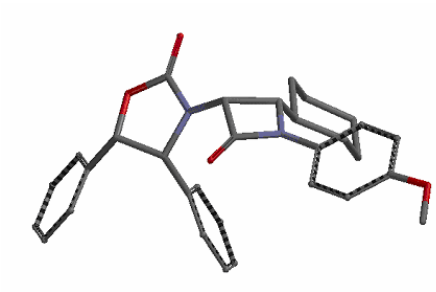
CALCULATED RELATIVE ENERGIES OF ALL FOUR ISOMERS OF LACTAM 27.

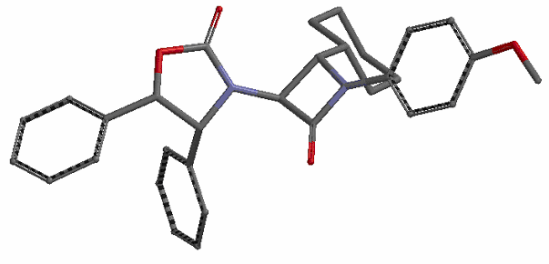


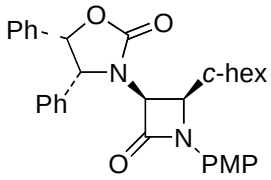
cis-**27a**



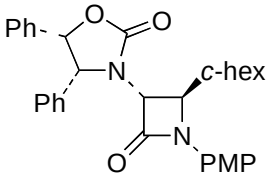
trans-**27a**



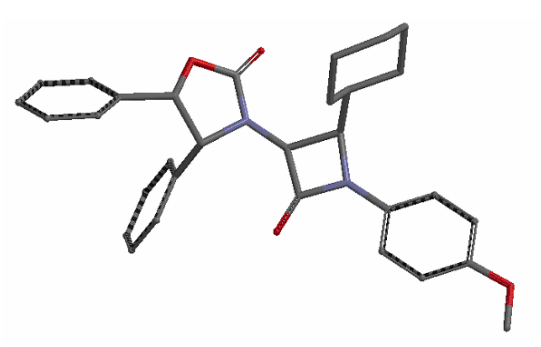


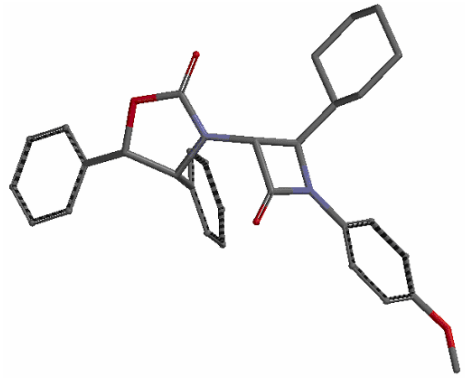


cis-**27b**



trans-**27b**





Model	relative energy (kcal mol^{-1})			
Structure	*cis*-**27a**	*trans*-**27a**	*cis*-**27b**	*trans*-**27b**
B3LYP/ 6-31G*	+3.98	+1.48	+4.86	0

Note: The relative energies of the structures were calculated with Spartan 06' software with B3LYP/ 6-31G* set.